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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 417/12, A61K 31/425	A1	(11) International Publication Number: WO 99/31094 (43) International Publication Date: 24 June 1999 (24.06.99)
(21) International Application Number: PCT/EP98/08154 (22) International Filing Date: 14 December 1998 (14.12.98) (30) Priority Data: 9726568.0 16 December 1997 (16.12.97) GB (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): BLACKLER, Paul, David, James [GB/GB]; SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN (GB). LEE, David, C. [GB/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB). SASSE, Michael, John [GB/GB]; SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN (GB). (74) Agent: RUTTER, Keith; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: HYDRATE OF 5-[4-[2- (N-METHYL-N- (2-PYRIDIL)AMINO) ETHOXY]BENZYL] THIAZOLIDINE-2, 4-DIONE MALEIC ACID SALT		
(57) Abstract A hydrate of 5-[4-[2- (N-methyl-N- (2-pyridyl)amino) ethoxy]benzyl] thiazolidine-2, 4-dione, maleic acid salt, characterised in that it: (i) comprises water in the range of from 0.2 to 1.1 % w/w; and (ii) provides an infrared spectrum containing peaks at 764 and 579 cm ⁻¹ ; and/or (iii) provides an X-ray powder diffraction (XRPD) pattern substantially as set out in Figure II; a process for the preparation of such a compound, a pharmaceutical composition containing such a compound and the use of such a compound or composition in medicine.		

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HYDRATE OF 5-[4-[2-(N-METHYL-N-(2-PYRIDIL)AMINO)ETHOXY]BENZYL]THIAZOLIDINE-2,4-DIONE MALEIC ACID SALT

5 This invention relates to a novel pharmaceutical, to a process for the preparation of the pharmaceutical and to the use of the pharmaceutical in medicine.

International Patent Application, Publication Number WO94/05659 discloses certain thiazolidinedione derivatives having hypoglycaemic and hypolipidaemic activity including 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt (hereinafter also referred to as "Compound (I)").

10 Compound (I) is disclosed solely as an anhydrous form. It has now been discovered that Compound (I) exists in a novel hydrated form which is particularly suitable for bulk preparation and handling. This can be prepared by an efficient, economic and reproducible process particularly suited to large scale preparation.

15 The novel hydrate also has useful pharmaceutical properties and in particular it is indicated to be useful for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

Accordingly, the present invention provides a hydrate of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt (the "Hydrate") characterised in that the Hydrate:

- 20 (i) comprises water in the range of from 0.2 to 1.1% w/w ; and
(ii) provides an infra red spectrum containing peaks at 764 and 579 cm^{-1} ; and/or
(iii) provides an X-ray powder diffraction (XRPD) pattern substantially as set out in Figure II.

25 Suitably, the water content of the Hydrate is in the range of from 0.4 to 0.9%w/w, especially 0.5 to 0.6% w/w, for example 0.54% w/w or 0.6 % w/w.

In one favoured aspect, the Hydrate provides an infra red spectrum substantially as set out in accordance with Figure I.

30 The Hydrate can exist in certain dehydrated forms which reversibly convert to the Hydrate when contacted with water, either in liquid or vapour form. The present invention encompasses all such reversibly rehydratable forms of the Hydrate.

The present invention encompasses the Hydrate isolated in pure form or when admixed with other materials, for example the known anhydrous form of Compound I, the above mentioned reversibly rehydratable forms or any other material.

35 Thus in one aspect there is provided the Hydrate in isolated form.
In a further aspect there is provided the Hydrate in pure form.

In yet a further aspect there is provided the Hydrate in crystalline form.

The invention also provides a process for preparing the Hydrate, characterised in that 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione,

maleic acid salt is crystallised from an aqueous alkanolic solvent, preferably containing from 2.0 to 2.5% by volume of water, most preferably 2.0 to 2.3%, for example 2.1 % by volume of water.

5 Suitable aqueous alkanolic solvents include aqueous ethanol, typically aqueous denatured ethanol, and aqueous isopropanol, or mixtures thereof.

 Crystallisation and any recrystallisation is generally carried out at low to ambient temperature, such as in the range of between 0 to 30°C for example 25°C; alternatively crystallisation may be initiated at an elevated temperature, such as in the range of between 30°C and 60°C for example 35°C, and then completed by allowing
10 the temperature of the solvent to cool to ambient or low temperature, such as in the range of between 0 to 30°C for example 25°C.

 The crystallisation can be initiated by seeding with crystals of the Hydrate but this is not essential.

 Compound I is prepared according to known procedures, such as those
15 disclosed in WO94/05659. The disclosures of WO94/05659 are incorporated herein by reference.

 When used herein the term 'prophylaxis of conditions associated with diabetes mellitus' includes the treatment of conditions such as insulin resistance, impaired glucose tolerance, hyperinsulinaemia and gestational diabetes.

20 Diabetes mellitus preferably means Type II diabetes mellitus.

 Conditions associated with diabetes include hyperglycaemia and insulin resistance, especially acquired insulin resistance and obesity. Further conditions associated with diabetes include hypertension, cardiovascular disease, especially atherosclerosis, certain eating disorders, in particular the regulation of appetite and
25 food intake in subjects suffering from disorders associated with under-eating, such as anorexia nervosa, and disorders associated with over-eating, such as obesity and anorexia bulimia. Additional conditions associated with diabetes include polycystic ovarian syndrome and steroid induced insulin resistance.

 The complications of conditions associated with diabetes mellitus
30 encompassed herein includes renal disease, especially renal disease associated with the development of Type II diabetes including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

 As used herein 'aqueous' with reference to a given solvent or solvent mixture,
35 refers to a solvent which contains sufficient water to provide Hydrate i.e having from 0.2 to 1.1 %w/w of water.

As mentioned above the compound of the invention has useful therapeutic properties: The present invention accordingly the Hydrate for use as an active therapeutic substance.

5 More particularly, the present invention provides the Hydrate for use in the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

The Hydrate may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier. The formulation of the Hydrate and dosages thereof are generally as disclosed for Compound (I) in
10 International Patent Application, Publication Number WO94/05659.

Accordingly, the present invention also provides a pharmaceutical composition comprising the Hydrate and a pharmaceutically acceptable carrier therefor.

The Hydrate is normally administered in unit dosage form.
15 The active compound may be administered by any suitable route but usually by the oral or parenteral routes. For such use, the compound will normally be employed in the form of a pharmaceutical composition in association with a pharmaceutical carrier, diluent and/or excipient, although the exact form of the composition will naturally depend on the mode of administration.

20 Compositions are prepared by admixture and are suitably adapted for oral, parenteral or topical administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, pastilles, reconstitutable powders, injectable and infusable solutions or suspensions, suppositories and transdermal devices. Orally administrable compositions are
25 preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tableting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents.
30 The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include
35 sodium lauryl sulphate.

Solid oral compositions may be prepared by conventional methods of blending, filling, tableting or the like. Repeated blending operations may be used to

distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the active compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the active compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the active compound.

In addition such compositions may contain further active agents such as anti-hypertensive agents and diuretics.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The present invention further provides a method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of Hydrate to a human or non-human mammal in need thereof.

Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

5 In the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof Hydrate may be taken in doses, such as those described above.

Similar dosage regimens are suitable for the treatment and/or prophylaxis of non-human mammals.

10 In a further aspect the present invention provides the use of Hydrate for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

No adverse toxicological effects are indicated for the compounds of the invention in the above mentioned treatments.

15 The following examples illustrate the invention but do not limit it in any way.

Example 1: Preparation of hydrate of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt.

- 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione free base (4.0 g) and maleic acid (1.40 g, 1.05 molar equivalents) were heated in denatured ethanol (40 ml) containing additional water (0.51 g, i.e. a total water content of approximately 2.1% (v/v)) to 60°C and held at this temperature for 30 minutes during which time a solution was obtained. The solution was filtered, re-heated to 50°C, and then cooled with stirring at a rate of 1 deg/min, resulting in crystallisation at 35°C.
- 10 The resulting suspension was cooled to 25°C and stirred for two hours. The product was filtered, washed with 99% denatured ethanol (8 ml) and dried at 50°C in vacuo for 24 hours to give the title compound (4.38 g, 82%). The water content of the product was 0.54% w/w.

- 15 **CHARACTERISING DATA:** The following characterising data was generated for the Hydrate:

A Infrared

- 20 The infrared absorption spectrum of a mineral oil dispersion of the Hydrate was obtained using a Nicolet 710 FT-IR spectrometer at 2 cm⁻¹ resolution. Data were digitised at 1 cm⁻¹ interval. The spectrum obtained is shown in Figure I. Peak positions are as follows: 3129, 2776, 1756, 1747, 1706, 1641, 1617, 1586, 1542, 1512, 1413, 1351, 1331, 1290, 1264, 1246, 1210, 1182, 1163, 1108, 1078, 1064,
- 25 1031, 1005, 975, 955, 926, 865, 764, 738, 719, 662, 619, 579, 557, 532, 525, and 508 cm⁻¹.

B X-Ray Powder Diffraction (XRPD)

- 30 The XRPD pattern of the Hydrate is shown below in Figure II and a summary of the XRPD angles and calculated lattice spacing characteristic of the Hydrate is given in Table I.

A PW1710 X-ray powder diffractometer (Cu X-ray source) was used to generate the spectrum using the following acquisition conditions:

- 35
- | | |
|--------------------|----------|
| Tube anode: | Cu |
| Generator tension: | 40 kV |
| Generator current: | 30 mA |
| Start angle: | 3.5 °2θ |
| 40 End angle: | 35.0 °2θ |
| Step size: | 0.020 |
| Time per step: | 4.550 s |

Table I.
X-Ray Powder Diffraction Angles and Calculated Lattice Spacing Characteristic of
the Hydrate.

5

Diffraction Angle (°2θ)	Lattice Spacing (Angstroms)
7.6	11.65
8.9	9.90
9.7	9.09
15.1	5.85
15.6	5.68
17.0	5.22
17.5	5.08
17.9	4.96
19.2	4.62
20.1	4.41
20.6	4.30
22.2	4.00
23.8	3.73
24.4	3.64
25.2	3.54
25.9	3.44
26.7	3.34
27.5	3.25
28.0	3.19
29.9	2.99
31.5	2.84

CLAIMS

1. A hydrate of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt., characterised in that it:
- 5 (i) comprises water in the range of from 0.2 to 1.1% w/w ; and
(ii) provides an infra red spectrum containing peaks at 764 and 579 cm^{-1} ; and/or
(iii) provides an X-ray powder diffraction (XRPD) pattern substantially as set out in Figure II.
- 10 2. A hydrate according to claim 1, wherein the water content is in the range of from 0.5 to 0.6%w/w.
3. A hydrate according to claim 1 or claim 2, which provides an infra red
15 spectrum substantially in accordance with Figure I.
4. A hydrate according to any one of claims 1 to 3, which provides an X-ray powder diffraction (XRPD) pattern substantially as set out in Figure II.
- 20 5. A hydrate according to any one of claims 1 to 4, in isolated form.
6. A hydrate according to any one of claims 1 to 5, in pure form.
7. A hydrate according to any one of claims 1 to 6, in crystalline form.
- 25 8. A compound in the form of a rehydratable form of a hydrate according to any one of claims 1 to 7.
9. A process for preparing a hydrate according to claim 1, characterised in that 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt is crystallised from aqueous ethanol.
- 30 10. A process according to claim 11, wherein the aqueous ethanol contains from 2% to 2.5% of water by volume.
- 35 11. A pharmaceutical composition comprising an effective, non-toxic amount of a hydrate according to claim 1 and a pharmaceutically acceptable carrier therefor.

12. A hydrate according to claim 1, for use as an active therapeutic substance.

13. A hydrate according to claim 1, for use in the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

14. The use of Hydrate for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

15. A method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of Hydrate to a human or non-human mammal in need thereof.

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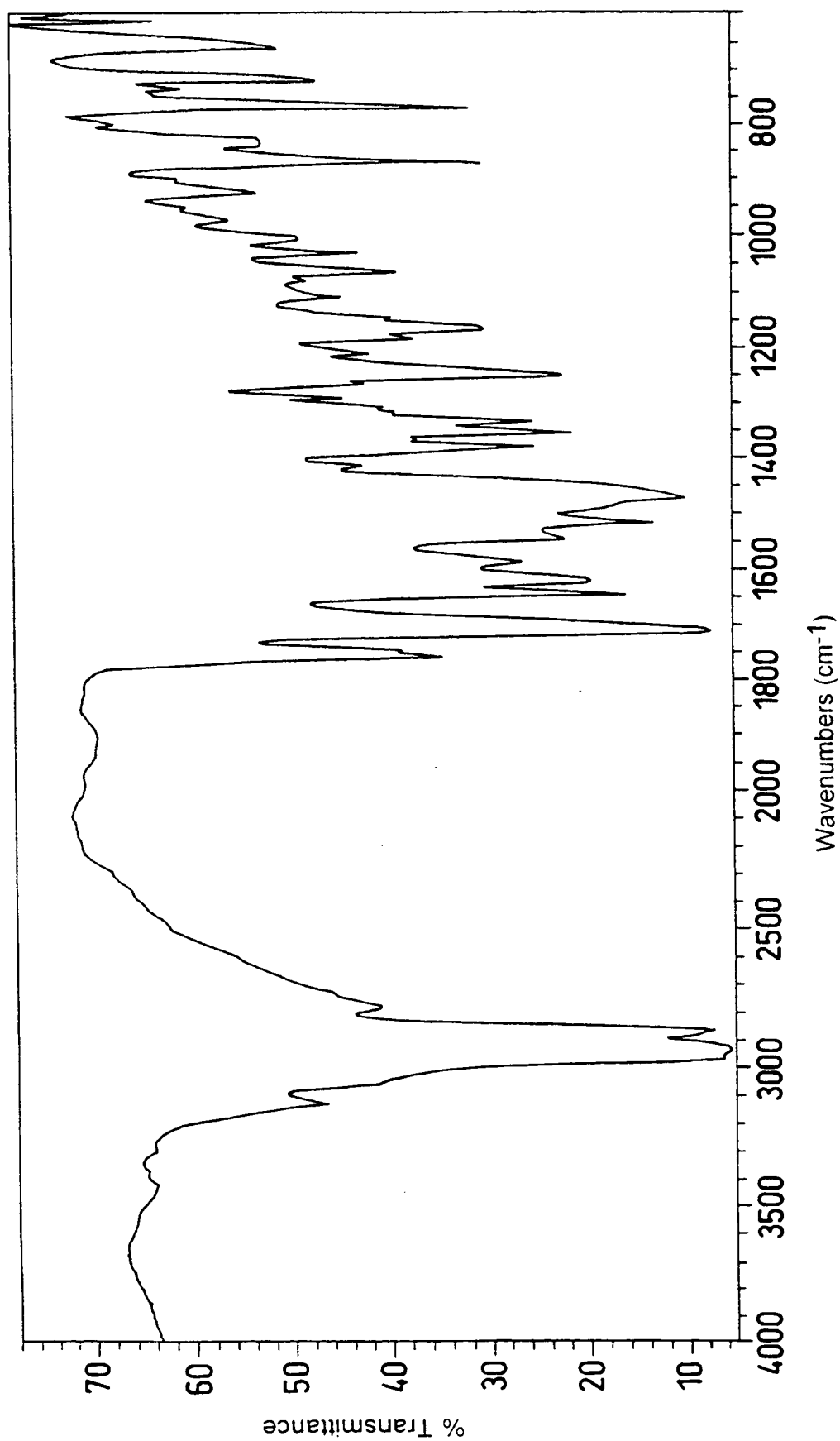


Fig. 1

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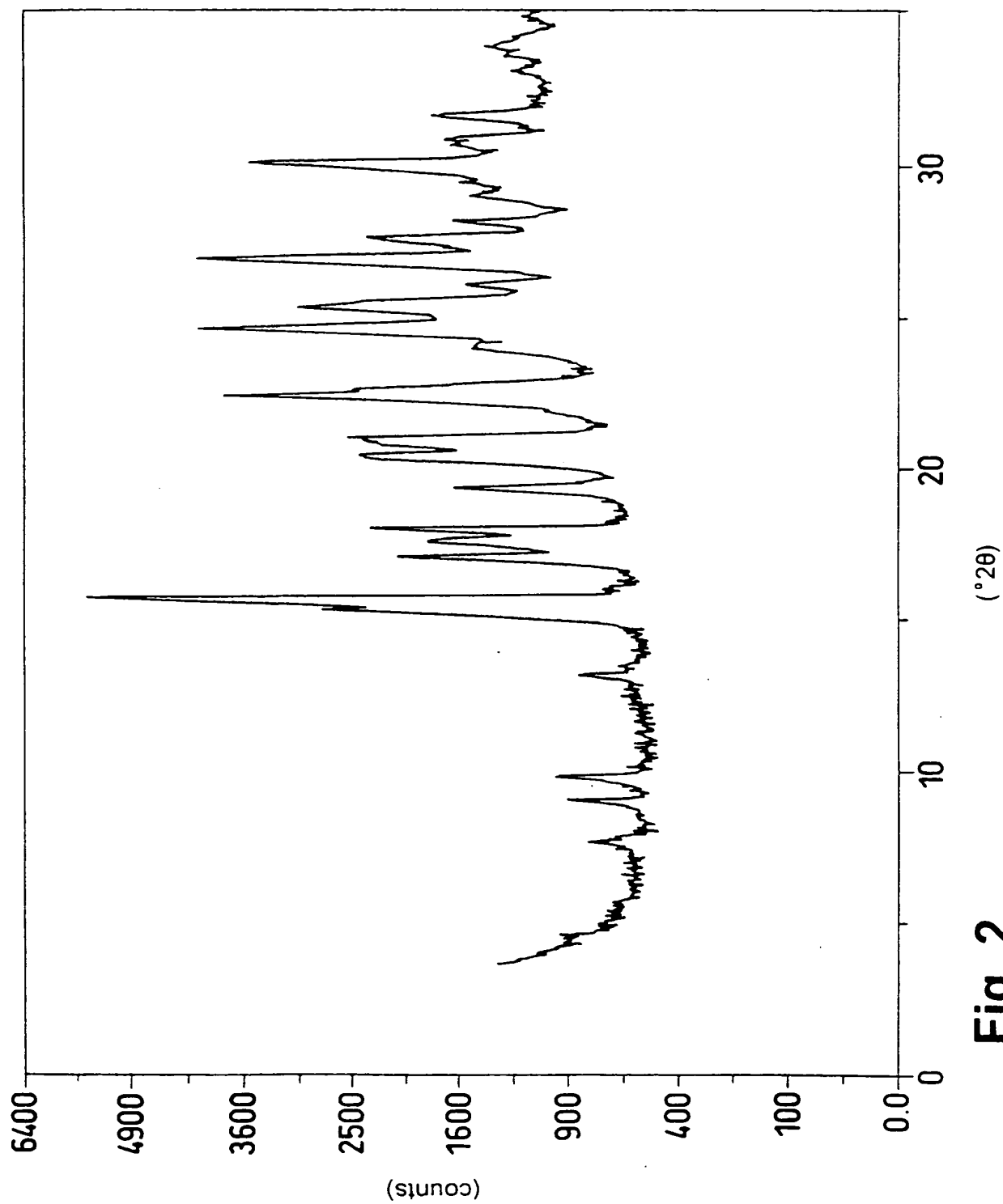


Fig. 2

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 98/08154

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D417/12 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 05659 A (SMITHKLINE BEECHAM PLC ; POOL COLIN RIPLEY (GB); ROMAN ROBIN SHERWO) 17 March 1994 cited in the application see page 3, line 32; example 1 ---	1-15
X	EP 0 306 228 A (BEECHAM GROUP PLC) 8 March 1989 see page 4, line 50; claim 1 -----	1-15

☐

Further documents are listed in the continuation of box C.

☒

Patent family members are listed in annex.

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Date of the actual completion of the international search

12 March 1999

Date of mailing of the international search report

19/03/1999

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INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/EP 98/08154

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9405659 A	17-03-1994	AU 674880 B	16-01-1997
		AU 4973093 A	29-03-1994
		CA 2143849 A	17-03-1994
		CN 1101911 A, B	26-04-1995
		CN 1183275 A	03-06-1998
		CN 1183413 A	03-06-1998
		CN 1183276 A	03-06-1998
		CZ 9500565 A	15-11-1995
		EP 0658161 A	21-06-1995
		FI 951004 A	03-03-1995
		FI 982413 A	06-11-1998
		HU 72639 A	28-05-1996
		IL 106904 A	30-09-1997
		JP 2828777 B	25-11-1998
		JP 8501095 T	06-02-1996
		MX 9305397 A	31-01-1995
		NO 950852 A	03-03-1995
		NO 974646 A	03-03-1995
		NZ 255505 A	22-08-1997
		PL 307812 A	26-06-1995
		SG 48302 A	17-04-1998
		SI 9300452 A	30-06-1994
		SK 27795 A	09-08-1995
		US 5741803 A	21-04-1998
		ZA 9306509 A	16-06-1994
EP 0306228 A	08-03-1989	AU 2173888 A	09-03-1989
		CA 1328452 A	12-04-1994
		CA 1339902 A	09-06-1998
		DK 490288 A	05-03-1989
		EP 0842925 A	20-05-1998
		JP 10194970 A	28-07-1998
		JP 10194971 A	28-07-1998
		JP 1131169 A	24-05-1989
		JP 2614497 B	28-05-1997
		JP 2817840 B	30-10-1998
		JP 9183771 A	15-07-1997
		JP 2837139 B	14-12-1998
		JP 9183726 A	15-07-1997
		JP 9183772 A	15-07-1997
		PT 88410 A, B	31-07-1989
		US 5646169 A	08-07-1997
		US 5002953 A	26-03-1991
		US 5521201 A	28-05-1996
		US 5232925 A	03-08-1993
		US 5194443 A	16-03-1993
		US 5756525 A	26-05-1998
		US 5260445 A	09-11-1993

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